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# **Contribution of Autonomic Nervous System to the Hypertension Induced by Obstructive Sleep Apnea**

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Rodrigo Iturriaga and Juan Idiaquez

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## **1. Introduction**

Cardiovascular diseases are the leading cause of morbidity and mortality in the adult population. The most common risk condition to almost all cardiovascular diseases is hypertension. The obstructive sleep apnea (OSA) syndrome, a growing worldwide sleep-breathing disorder is recognized as an independent risk factor for hypertension and is associated with other cardiovascular diseases, such as stroke, pulmonary hypertension, coronary artery disease and stroke. OSA is characterized by repeated episodes of airflow detention during sleep produced by the upper airway collapse. Among the disturbances produced by OSA, the chronic intermittent hypoxia is considered the main factor for the progression of the systemic hypertension. Although the link between OSA and systemic hypertension is well established, the pathogenic mechanisms responsible for the hypertension are not entirely understood. Autonomic dysfunction, oxidative stress and inflammation have been proposed as potential hypertensive mechanisms. However, conclusions from studies in OSA patients are controversial, because of concomitant comorbidities (i.e. obesity, metabolic disorders and cardiovascular diseases), which are confounding factors that increases the cardiovascular risk associated with OSA. Thus, experimental models of rodents exposed to chronic intermittent hypoxia, which reproduced several pathologic cardiovascular features of OSA, are the gold-standard to study the pathogenic mechanisms involved in the OSA-induced hypertension. In this chapter, we will review and discuss the evidence supporting an essential role of the carotid body chemoreceptor and the contribution of the autonomic nervous system to the progression of the hypertension in OSA patients and animals exposed to chronic intermittent hypoxia.

## 2. Pathogenic mechanisms of the hypertension induced by OSA

The OSA syndrome elicited by repeated airflow total or partial occlusions is diagnosed when patients has an apnea-hypopnea index (AHI) > 10 events/hour. OSA affects up to 9% of the adults men and 4% of women worldwide population [111]. However, according to a report of the American Heart Association in collaboration with the National Center on Sleep Disorders Research, “85% of patients with clinically significant and treatable OSA have never been diagnosed, and referral populations of OSA patients represent only the *tip of the iceberg* of OSA prevalence”. Therefore, the estimated adult population that present an AHI of 5 is ~20% [100]. The OSA syndrome is associated with clinical neurobehavioral dysfunction, such as daytime sleepiness, fatigue, depressed mood, attention and executive deficits, and verbal and visual-spatial memory impairments [5, 67]. Nevertheless, the OSA syndrome is also associated with diurnal systemic hypertension (~50% of the OSA patients developed systemic hypertension), and with stroke, pulmonary hypertension, coronary artery disease and atrial fibrillation [3, 8, 12, 19; 28, 30, 35, 52, 53, 64, 74, 79, 100].

Several epidemiological studies have shown that OSA is an independent risk factor for the progression of the hypertension. Indeed, OSA patients show a positive relationship between AHI and the hypertension, which is independent of other risks [23, 60, 61, 85, 96, 100, 111, 112]. Moreover, results obtained from the Wisconsin Sleep Cohort (an ongoing 21-years longitudinal study performed on 1500 Wisconsin state employees) have shown that untreated OSA patients have a high mortality risk associated with AHI [74, 112].

Although the link between OSA and hypertension is well established, the mechanisms underlying the hypertension are not entirely known. The most accepted explanation proposes that chronic intermittent hypoxia produces oxidative stress, inflammation, and sympathetic hyperactivity, which led to endothelial dysfunction and hypertension [19, 25, 28, 41, 43, 52, 53, 65, 99, 100], but it is likely that intrathoracic pressure changes causing excessive mechanical stress on large artery walls and the heart, and arousal-induced sympathetic hyperactivity may also contribute to the endothelial dysfunction [47]. OSA is characterized by repeated episodes of total or partial airflow detention during sleep produced by the pharyngeal collapse, eliciting intermittent hypoxia and hypercapnia, negative intrathoracic pressure, sleep fragmentation and arousal. During the airflow occlusion, the resulting hypoxia and hypercapnia stimulates the carotid body chemoreceptors producing reflex ventilatory, sympathetic and hypertensive responses. Among these disturbances, the chronic intermittent hypoxia is considered the main factor for the development of the hypertension [1, 19, 33, 41, 43, 51, 55, 56, 82, 83, 88, 93, 100]. However, conclusions from studies performed in OSA patients are partial and somehow controversial, because invasive procedures are precluded because of ethical reasons in humans, and OSA patients often present concomitant morbidities (i.e. obesity, metabolic alterations and other cardiovascular diseases), which are confounding factors that increase the cardiovascular risk. Therefore, experimental models of rodents exposed to intermittent hypoxia, which simulates the hypoxic-reoxygenation cycles and reproduce several of the cardiovascular pathologic features of OSA including hypertension, are the gold-standard to

study the pathogenic mechanisms involved in progression of the cardiovascular and respiratory alterations induced by OSA [15-18, 22, 27, 43, 83-84, 86, 88, 95].

### 3. Clinical aspects of OSA

There are a strong association between OSA and systemic hypertension in human patients. Indeed, several studies have shown that the prevalence of OSA is higher in hypertensive patients, while other studies have shown that OSA increases the predisposition for hypertension. In addition, there are observational studies that showed that patients with hypertension presented a high incidence of OSA, some of these studies are cross-sectional [27, 46, 51, 109]. It has been found in patients with resistant hypertension, that the main secondary cause was OSA [81]. On other hand, cross-sectional studies have shown that patients with sleep breathing disorders, including OSA and snoring, present a strong correlation with hypertension [8, 74, 112]. Prospective studies also showed a strong association between AHI and THE increased arterial blood pressure [85]. It is relevant to note that the OSA-hypertension link is independent from other comorbidities like obesity [33, 45, 51, 79, 100]. Other study performed in OSA patients without hypertension, which were follow-up during five years for the risk of hypertension, concluded that there is a trend of association between AHI > 30 and the occurrence of the hypertension [75]. OSA patients without treatment presented high risk of hypertension than those patients treated with continuous positive airway pressure (CPAP) therapy [61].

OSA and hypertensive patients frequently present a combination of comorbidities including obesity, diabetes and cardiovascular diseases ([1, 33, 45, 54, 56, 64, 100]. The mechanisms that could explain the association between OSA and hypertension are still in ongoing research. As was mentioned before, the pathogenesis of the association between OSA and hypertension is likely to be multifactorial, involving a varied range of pathogenic mechanisms comprising a group of systemic factors including inflammation, oxidative stress and metabolic dysregulation, which are beyond the scope of this review. Evidence supporting the role played by sympathetic dysfunction has been demonstrated by different invasive and noninvasive methods that quantify sympathetic activity in patients with OSA, the main methods reported are:

#### 3.1. Muscle sympathetic nerve activity in OSA patients

This technique is based on the microneurographic recording with a tungsten electrode of the muscle sympathetic nerve activity in the peroneal nerve, which produce vasoconstriction in blood vessel of skeletal muscles. The muscle sympathetic nerve discharge plays a fundamental role in the homeostasis of the systemic arterial blood pressure. Studies comparing muscle sympathetic discharges between OSA patients and controls showed that patients had higher basal levels of muscle sympathetic nerve discharges [71-73, 99]. Also intermittent hypoxia in humans produced hypertension and elevated the muscle sympathetic nerve discharges [29]. Continuous positive air pressure therapy decrease muscle sympathetic nerve discharges overactivity in OSA patients [39, 72, 73, 99].

### 3.2. Heart rate variability in OSA patients

The spectral analysis of heart rate variability has two major components defined as the low frequency (LF) band related to sympathetic influences, and the high frequency (HF) band related mainly to vagal influences and respiratory sinus arrhythmia. The LF/HF ratio is believed to be an index of the sympathovagal balance on heart rate [105]. Normotensive patients with recently diagnosed OSA showed a shift of the HRV spectral indexes towards the low frequency band, which is associated with increased sympathetic discharges in the peroneal nerve [70, 97]. The spectral analysis of heart rate variability is performed using a Fast Fourier Transform or autoregressive methods. The spectrum of R-R intervals is assessed using the following frequency bands: very low frequency: DC-0.04 Hz, low frequency (LF): 0.04-0.15 Hz and high frequency (HF): 0.15-0.4 Hz in the frequency domain. HF power reflects the activity of parasympathetic nervous system activity, whereas LF power reflects a combination of sympathetic and parasympathetic activity [92, 105]. OSA patients showed increased sympathetic and reduced vagal modulation of HRV in comparison with controls [2, 4]. This sympatho-vagal imbalance is modified with CPAP therapy; in OSA patients with hypertension CPAP administration reduced the LF power [11, 114].

### 3.3. Catecholamine measurements in OSA patients

The measurement of blood or urinary catecholamines gives information about their release from neurons and from the adrenal medulla. Baseline values of the plasmatic concentration of norepinephrine (NE) characterize the balance between the amount of NE released and then re-uptake into the nerve terminals. The urinary NE is the amount of NE that is being eliminated by excretion and metabolism. Plasmatic concentration of epinephrine (E) represents a balance between adreno-medullary release, excretion and metabolism. In OSA patients, studies of catecholamines concentrations had shown the presence of elevated levels of catecholamines in plasma and urine [62, 24, 113], suggesting an elevated sympathetic activity. OSA patients with elevated NE levels in plasma and urine showed severe hypertension and excessive sweating, similar to what happened in pheochromocytoma, improved their condition with CPAP therapy ([36]. It has also been shown that CPAP reduces NE levels in patients with severe OSA [101, 113, 114]. In children with OSA an association between AHI and urinary NE and E has been also reported [76].

### 3.4. Noninvasive cardiovascular autonomic tests in OSA patients

These tests are grouping in two main categories: sympathetic and cardiovagal tests. The sympathetic tests include arterial blood pressure response to gravitational stress, isometric exercise and cold stimuli. Cardiovagal autonomic tests include heart rate changes on deep breathing, Valsalva maneuver ratio and heart rate changes on standing. These tests are performed during wakefulness and they have shown a diurnal sympathetic dysfunction [6, 14, 66, 103]. Also parasympathetic cardiac dysfunction has been found in OSA patients [14, 66, 107]. Overall, the results of these tests suggest an increased sympathetic tone and a decreased parasympathetic cardiac function in OSA patients.



#### **4. Autonomic dysfunction in animals exposed to chronic intermittent hypoxia**

Patients recently diagnosed with OSA, show enhanced vasopressor and ventilatory responses to acute hypoxia [69, 71], sympathetic hyperactivity, demonstrated by an increased muscle sympathetic neural activity [9, 68, 72-73, 99] and a higher accumulation of 24-h urinary norepinephrine [21]. Similarly, animals exposed to chronic intermittent hypoxia present enhanced sympathetic discharges and respiratory responses to acute hypoxia, and develop systemic hypertension [15, 20, 25, 26, 34, 37, 48, 59, 86, 87, 92, 115]. The autonomic alteration is characterized by an enhanced sympathetic outflow, reduction of the efficiency of the baroreflexes sensitivity and alterations of heart rate variability. Indeed, non-invasive spectral analysis of heart rate variability suggested a preponderance of the sympathetic drive in animals exposed to chronic intermittent hypoxia [15, 20, 57, 86, 88, 92], similarly to what was observed patients with OSA [68,72, 97,99]. Thus, it is likely that the enhanced sympathetic activity along with the reduction of the baroreflex sensitivity could impair heart rate variability and the regulation of vasomotor tone of blood vessels contributing to the hypertension. In addition, chronic intermittent hypoxia elicits vagal withdrawal, attributed in part to neuronal loss in ambiguous nucleus [57, 110].

Using a protocol of short hypoxic cycles (10% O<sub>2</sub>, 10 times/hr for 8 hrs), we found that exposure of cats to chronic intermittent hypoxia for 4 days enhanced the ventilatory responses induced by acute hypoxia and reduced the sensitivity of the baroreflex control of heart rate, but did not evoke hypertension or enhanced the vasopressor responses to hypoxia [88, 90, 92]. However, normotensive animals exposed to chronic intermittent hypoxia like normotensive OSA patients, show a similar increased LF/HF ratio [88, 92]. Besides that, we found a positive linear correlation ( $r=0.97$ ) between the LH/HF ratio and the baseline carotid body chemosensory discharges in the hypoxic-treated cats, suggesting that the potentiation of carotid body chemosensory discharges may be linked to early changes in the autonomic control of heart rate in cats exposed to short-term chronic intermittent hypoxia [92]. Thus, our results suggest that the hypertension induced by chronic intermittent hypoxia is preceded by early alterations in the autonomic balance of the heart rate, associated with an enhanced carotid body chemosensory response to hypoxia and a decreased baroreflex control [88, 92]. Lai et al., [See in 49] also found that chronic intermittent hypoxia increases the LF component and the LF/HF ratio of the blood pressure variability before the onset of the hypertension in conscious rats exposed to intermittent hypoxia.

#### **5. Contribution of the carotid body to the cardiorespiratory alterations in OSA patients and animals exposed to chronic intermittent hypoxia**

The enhanced cardiorespiratory responses to acute hypoxia observed in OSA patients has been attributed to a potentiated hypoxic peripheral chemoreflexes [12, 58, 69, 71], suggesting that carotid body chemoreceptors play a main role in the pathological alterations induced by OSA.

Moreover, Fletcher et al., [See in 26] found that the bilateral carotid body denervation prevented the hypertension in rats exposed to chronic intermittent hypoxia, suggesting that the carotid body contributes to the cardiovascular pathologies induced by OSA. In the last years, the proposal that the carotid body is involved in the progression of the intermittent hypoxia-induced hypertension received substantial attention [19, 22, 25, 28, 41, 43, 98, 100].

A growing body of new evidence supports the proposal that the carotid body is involved in the generation of the hypertension in OSA patients and animals exposed to intermittent hypoxia. OSA patients present enhanced ventilatory, pressor and sympathetic responses to acute hypoxia, attributed to a potentiation of the peripheral hypoxic chemoreflexes [58, 100]. Narkiewicz et al. [See in 69, 71] studied the reflex ventilatory, tachycardic and vasopressor responses to acute hypoxia in untreated normotensive patients with OSA, and found that the hypoxic stimulation produce larger increases in volume-minute ventilation, heart rate and arterial blood pressure in OSA patients than control subjects. Thus, the available data support the idea that the enhanced chemoreflex response observed in OSA patients is produced by the intermittent hypoxia. Similarly, animals exposed to chronic intermittent hypoxia show enhanced hypoxic ventilatory responses to acute hypoxia [15, 18, 43, 44, 87] and long-term facilitation of respiratory motor responses [63, 83, 88]. Recording of chemosensory nerve impulses from the carotid sinus nerve have confirmed the idea that chronic intermittent hypoxia produces long-term facilitation of the carotid body chemosensory responses to hypoxia. Indeed, exposure of rats and cats to intermittent hypoxia for few days increases the basal carotid body discharges measured in normoxia and enhances the chemosensory responses to acute hypoxia [15, 18, 43, 82-84, 88, 90].

The carotid body, located in the bifurcations of the carotid arteries is the main arterial oxygen chemoreceptor in terms of its contribution to the ventilatory reflex responses. In mammals, the hypoxic stimulation of the carotid body increases the sympathetic discharges to the arterial blood vessels and heart, producing hypertension. The primary oxygen sensors in the carotid body are the glomus cells, which are in synaptic contact with the nerve terminals of the chemosensory petrosal neurons [31, 40, 42]. The current model of chemoreception states that hypoxia induces the inhibition of voltage-independent tandem pore domain potassium channels (TASK  $K^+$ ), leading to the depolarization of the glomus cells, the entry of  $Ca^{2+}$  through L-type  $Ca^{2+}$  channels, and the subsequent release of excitatory transmitters (Acetylcholine and adenosine triphosphate), which increases the discharges of the nerve endings of the petrosal chemosensory neurons [40, 42]. Recently, we found that chronic intermittent hypoxia potentiates the hypoxic inhibition of the TASK-like  $K^+$  channel currents in glomus cells from intermittent hypoxia rats. This novel effect of intermittent hypoxia may contribute to explain its enhancing effect on carotid body hypoxic chemoreception [77]. The carotid body is a polymodal chemosensory receptor, which is activated by hypoxia, hypercapnia, acidosis, stop flow, temperature and respond to the levels of glucose [31]. The carotid body has been involved in several sympathetic-mediated diseases such as hypertension, heart failure, diabetes and renal failure [94]. Moreover, the denervation or ablation of the carotid body has been proposed for the treatment of severe and resistant hypertension [78].

## 6. Mediators of enhanced carotid body chemosensory responses to hypoxia in animal models of OSA

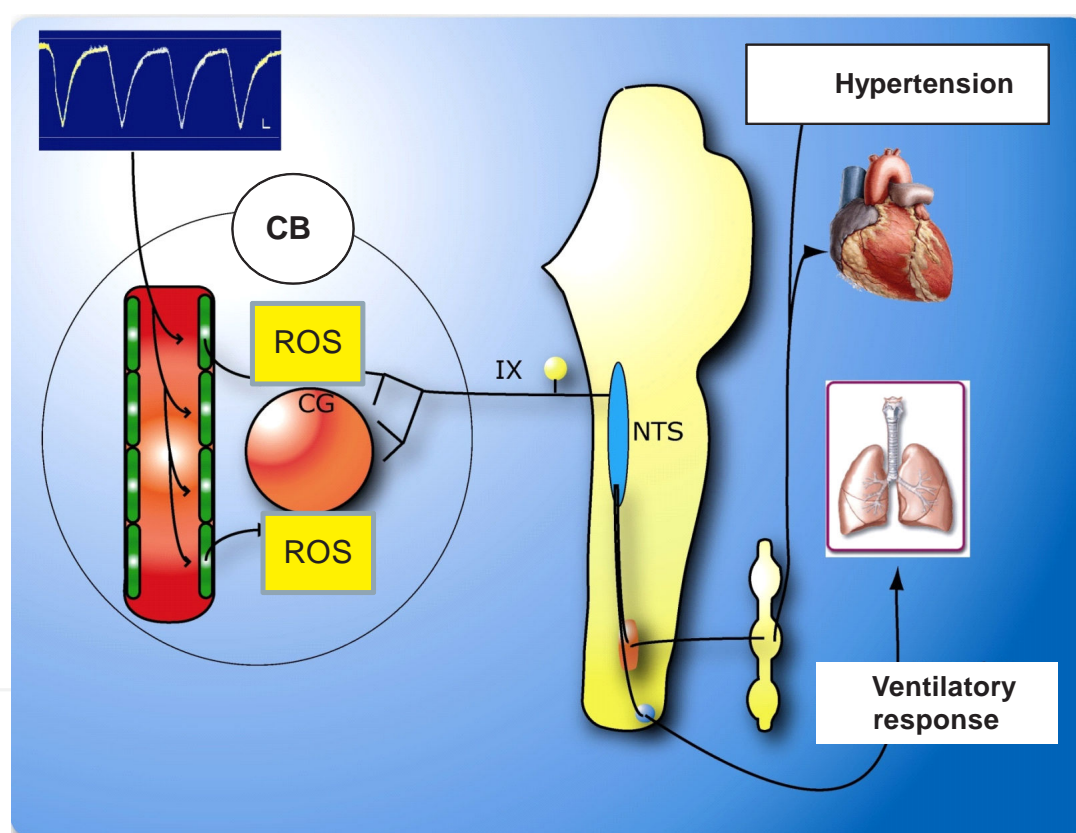
Reactive oxygen species (ROS) and reactive nitrogen species (RNS), and pro-inflammatory agents have been proposed as mediators of cardiovascular and cognitive alterations in OSA patients [7, 13, 33, 45, 52, 65, 102] and animal models [10, 15-18, 44, 48, 82, 84, 106]. Studies performed in OSA patients and animals exposed to intermittent hypoxia showed that the hypoxia-reoxygenation episodes produce systemic oxidative stress due to the accumulation of ROS and RNS, which are potential sources of cellular damage. Recently, we tested the hypothesis that oxidative stress contributes to the carotid body chemosensory potentiation and the progression of the hypertension in rats exposed to chronic intermittent hypoxia [15, 18, 44]. We found that intermittent hypoxia increased the plasma lipid peroxidation and the formation of the oxidative stress marker 3-nitrotyrosine in the carotid body. In addition, chronic intermittent hypoxia enhances carotid body chemosensory and reflex ventilatory responses to hypoxia, alters heart rate variability and elicits hypertension [15]. Ascorbic acid treatment reduced the increased systemic and local carotid body oxidative stress, the potentiation of the carotid body chemosensory and ventilatory responses to hypoxia, as well as the hypertension [15]. These results agree and extend previous observations that antioxidant pretreatment prevented the carotid body chemosensory potentiation [80, 82] and the hypertension [106] in rats exposed to intermittent hypoxia. Although, these results strongly suggest that the carotid body chemosensory potentiation is mediated by oxidative stress [15, 43, 44, 80], it is a matter of debate if ROS *per se* increases the carotid body chemosensory discharges [32]. Thus, it is likely that other molecule downstream the ROS signals mediate the effects of ROS on carotid body chemoreception induced by intermittent hypoxia. The CB, the main contributor to the sympathetic activation and hypertension following intermittent hypoxia is extremely sensitive to peroxynitrites formation [15]. Thus, RNS formation is a common feature in both human and experimental OSA models, suggesting that may participate in the OSA pathophysiology. In conclusion, the available evidence supports and extends the idea that both oxidative and nitrosative stress plays a pivotal role in OSA pathophysiology.

Among the molecules upregulated in the carotid body by intermittent hypoxia, such as endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), and inducible nitric oxide synthase (iNOS) [15-18, 50, 89-91], pro-inflammatory cytokines have been proposed as mediators of the carotid body chemosensory potentiation induced by intermittent hypoxia [16, 18, 43, 44, 50] and cardiovascular pathologies in OSA patients [7, 65, 108, 104]. We found that chronic intermittent hypoxia induced a ROS-dependent increases of tumor necrosis factor (TNF) and Interleukin 1 $\beta$  (IL-1 $\beta$ ) in the carotid body, suggesting that these pro-inflammatory cytokines may mediate the ROS-induced carotid body potentiation [16, 18]. To test this hypothesis, we studied the effects of ibuprofen on the increased TNF- $\alpha$  and IL-1 $\beta$  levels in the rat carotid body, the potentiation of carotid body chemosensory and ventilatory hypoxic responses and the hypertension [18]. Ibuprofen prevented the carotid body cytokines overexpression, the enhanced hypoxic ventilatory response and the hypertension, but failed to block the enhanced carotid body chemosensory responses. Thus, our studies suggest that the



upregulation of  $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$  in the carotid body induced by chronic intermittent hypoxia is linked to oxidative stress, as well as the enhanced carotid body chemosensory responsiveness to hypoxia, but the chemosensory potentiation does not depend on the increased  $\text{TNF-}\alpha$  and  $\text{IL-1}\beta$  levels in the carotid body [18]. However, pro-inflammatory cytokines contribute to enhance the hypoxic ventilatory response and the hypertension induced by chronic intermittent hypoxia, suggesting that multiple mechanisms may participate in the cardiorespiratory alterations induced by intermittent hypoxia [18]

Figure 1 shows a diagram of the proposed contribution of the intermittent hypoxic induced potentiation of CB chemosensory hypoxic responsiveness to the hypertension. It is likely that the hypoxic-reoxygenation cycles enhance the CB chemosensitivity to hypoxia, which in turn contributes to elicit a persistent augmented sympathetic neural output.



**Figure 1.** Diagram of the contribution of the carotid body (CB) to the hypertension induced by chronic intermittent hypoxia. ROS, reactive oxygen species. NTS, nucleus of the tractus solitarius. CG, chemoreceptor (glomus) cells.

## 7. Conclusion

OSA patients and animals exposed to chronic intermittent hypoxia show autonomic alterations and a potentiated carotid body chemosensory response to hypoxia. The autonomic alterations are characterized by an enhanced sympathetic outflow, a reduction of the efficiency

of the baroreflexes sensitivity and alterations of heart rate variability. Indeed, non-invasive spectral analysis of heart rate variability shows a predominance of the sympathetic drive in patients with OSA and animals exposed to intermittent hypoxia. Moreover, direct recordings of muscle nerve sympathetic discharges also showed an increased sympathetic tone and response to hypoxia. Thus, it is likely that the enhanced sympathetic activity along with the reduction of the baroreflex sensitivity could impair heart rate variability and the regulation of vasomotor tone of blood vessels eliciting sustained blood pressure elevation.

Studies performed in OSA patients and animals models exposed to chronic intermittent hypoxia have provide evidence that OSA is associated with enhanced sympathetic activation, mainly attributed to the chronic intermittent hypoxia. The link between the cardiovascular consequences of OSA, including hypertension is multifactorial, most likely related to enhanced sympathetic activity, but also with oxidative stress and systemic inflammation. Understanding how the autonomic dysfunction induced by intermittent hypoxia interacts with metabolic alterations, oxidative stress and inflammation will provide new insights into the pathogenesis of the hypertension associated with OSA. Further basic knowledge will allow proposing and developing new therapeutic strategies to moderate the severity of the cardiovascular alterations induced by OSA.

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## Author details

Rodrigo Iturriaga<sup>1\*</sup> and Juan Idiaquez<sup>2</sup>

\*Address all correspondence to: [riturriaga@bio.puc.cl](mailto:riturriaga@bio.puc.cl)

1 Laboratorio de Neurobiología, Departamento de Fisiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile

2 Escuela de Medicina, Universidad de Valparaíso, Valparaíso, Chile

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